

Original Article

COMPARISON OF TB INCIDENCE OF YOUNG AND MIDDLE AGE GROUPS
BETWEEN URBAN/SUBURBAN PREFECTURES AND OTHER PREFECTURES

Hitoshi HOSHINO, Kazuhiro UCHIMURA, and Yuko YAMAUCHI

Abstract [Purpose] Comparison of TB incidence in young and middle age group between urban/surrounding area and other area.

[Material & Methods] TB incidence in young and middle age group by sex, nationality, labor status and prefecture is calculated with data of National Population Survey and TB surveillance in 2005. Risk factors of TB infection/break down such as public transportation, poverty, population density, diabetes, malignancy, HIV infection, foreigners are compared between urban/surrounding area and other area.

[Results] TB incidence of employees, jobless and housekeepers in urban/surrounding prefectures is higher than other prefectures, but TB incidence of housekeepers is low and difference is small. Utilization frequency of public transportation is correlated with prefectural level of TB incidence of male and female employees. There is no correlation with prevalence of other risk factors.

[Discussion] Public transportation and working in urban area is indicated as causes of difference of TB infection risk. Reinforcement of TB control program of working places in urban area is important and if necessary contact survey of TB outbreak at public transportation should be considered. Further analysis using more precise indicators is necessary to elucidate for influence of poverty.

Key words: Tuberculosis, Incidence, Urban area, Poverty, Risk factor

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PROBLEMS IN MODEL-BEDS FOR TUBERCULOSIS PATIENTS

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Abstract [Purpose] To investigate the possibility and obstacles to care tuberculosis patients in general hospitals.

[Object & Method] Sending questionnaire to the general and psychiatric hospitals running the model-beds for tuberculosis patients care, which have been the project proposed by Ministry of Health, Labour and Welfare, and analyzing their answers.

[Result] Answer sheets were recovered from 43 of 75 (57%) hospitals which were the objects of this investigation. Situations of running the model-beds were highly diverse. 74% of the hospitals assumed that the general hospitals (, if some conditions were satisfied,) could care most of the tuberculosis patients. Problems in running the model-beds pointed by the hospitals were ; HIC (hospital infection control) procedures pressing extra-workload (37%), low occupancy rate of the model-beds (30%), high cost of equipments for HIC (28%), high workload and high cost for tuberculosis patients care (21%), low fee for tuberculosis care (16%), difficulties of caring psychologically and/or physically unstable tuberculosis patients in rooms separate from the nurse station (16%), difficulties in long-term in-hospital care due to lack of sufficient amenities (14%), difficulties in accepting tuberculosis patients with short notice (12%), heavy burden for nurses who have to

care for patients with associated conditions unfamiliar to them (12%), difficulties in maintaining quality of tuberculosis care (7%), risk of infection to the staffs and other patients (5%) and others miscellaneous problems (16%).

[Conclusion] Needs for tuberculosis patients' care in general hospitals are expected to further increase in the near future, but to cope with the above situation many problems are still to be solved. Hereafter we must expand the project of model-beds for tuberculosis care, and accumulate more experiences in tuberculosis patients' care in general hospitals.

Key words: Tuberculosis ward, General ward, Co-morbidity, Hospital infection control, TB care unit

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Original Article

EVALUATION OF THE INNO-LiPA MYCOBACTERIA v2 FOR MYCOBACTERIAL IDENTIFICATION

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²Motohisa TOMITA, ¹Masaji OKADA, and ³Mitsunori SAKATANI

Abstract [Purpose] Evaluation of the INNO-LiPA MYCOBACTERIA v2 (the INNO-LiPA assay) for mycobacterial identification.

[Materials and Methods] The laboratory identifications consisting of Cobas Amplicor systems, AccuProbe, and DDH, are commonly used to identify mycobacterial isolates in Japan. We compared the results between the INNO-LiPA assay and the common methods. A total of 122 clinical isolates from NHO Kinki-chuo Chest Medical Center from 1 February to 30 June 2006 were tested.

[Results] There was agreement between the INNO-LiPA assay and the common methods for 112 mycobacterium isolates. The six discordant isolates have showed same results between sequencings and the INNO-LiPA assay. The one *M. fortuitum* isolates was indicated correctness by DDH and the one *M. intracellulare* isolates was recognized by Cobas Amplicor systems and as MAC by AccuProbe MAC. Moreover, discrepant results between sequencings and mycobacterial identifications including the INNO-LiPA assay

were 2 isolates (*M. paraffinicum*, *M. mucogenicum* variant type).

[Conclusion] The INNO-LiPA assay could provide rapid and correct identification results with clear-cut and easy interpretation.

Key words: Mycobacteria, INNO-LiPA MYCOBACTERIA v2, Identification, 16S rRNA gene, ITS sequencing

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Report and Information

START OF PTB (PHTHISIS) MORTALITY STATISTICS IN JAPAN (2)

Tadao SHIMAO

Abstract As mentioned in the previous report, PTB mortality by prefecture was printed in the “Statistics Annual”, however, the population based on which the rate was calculated was not shown in the “Statistics Annual”. In Japan, family register system was introduced in 1872, and every Japanese had to be registered at municipality where their family live. Based on this registry, statistics on registered population by sex and age, and by prefecture was available.

In case when some family member(s) move to place other than registered place, he/she has to report to the local municipality in which they reside. When they move further to other place, the same procedure was required. Population based on this temporary registration system was named as A-type population, however, it did not show the population actually living in the municipality.

Many persons newly register when they move in, however, forget to report to the previous residence when they move out. Overall numbers of move-in always larger than move-out. To adjust for this discrepancy and to estimate actually living population by each prefecture, the difference of move-in and move-out in a certain prefecture was multiplied by the ratio of total move-in and move-out in a certain prefecture and that of the whole country. Thus calculated population was designated as B-type population, and was proximate to actually living population in each prefecture.

As B-type population was tabulated by sex in each prefecture, PTB mortality by sex could be calculated by using this B-type population, and the calculated figures were shown in Table 3 by sex for each prefecture. The correlation between PTB mortality by prefecture printed in the “Statistics Annual” and that calculated by using B-type population in 1886, 1892

and 1899 were shown in Fig. 4. Both coincide well nearly in all prefectures, except Tokyo and Hokkaido in 1886 and 1892, and in Tokyo in 1899. It was shown how difficult it was to estimate actually living population in an area where population move was very active, however, in general, in other prefectures both coincided well, and figures shown in Table 3 could be used to estimate PTB mortality in each prefecture by sex.

Since 1899, ICD (International Classification of Diseases) was adopted in Japan as causes of death, and TB of all forms were divided into PTB, TB meningitis, intestinal TB and TB of other organs. As phthisis mortality was also available in 1899, correlation between PTB (Phthisis) mortality and that of TB of all forms was shown in Fig. 5 by age groups and by prefecture. The former was higher than the latter, and observing by age groups, correlation was not good in infants and elder population 60 years and over. In large cities like Tokyo and Oosaka, figures of the former were higher than the latter. It was indicated that it was not appropriate to combine and analyze the trend of PTB (Phthisis) mortality with the TB mortality statistics after 1899 adopting ICD.

Key words: A-type population, B-type population, PTB (Phthisis) mortality by sex and prefecture, Correlation between Phthisis mortality and mortality of TB of all forms

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————— The 83rd Annual Meeting Symposium —————

INFECTION OF TUBERCULOSIS: ESTIMATION OF THE MAGNITUDE AND INVESTIGATION OF THE PLACE OF THE RISK

Chairpersons: ¹Makoto TOYOTA and ²Takashi YOSHIYAMA

Abstract: With this symposium, we focused on the infection. The infection is the source of tuberculosis diseases and at the same time, it is the result of tuberculosis diseases. We understand that tuberculosis has reduced, but we have rough idea how is the risk of infection in Japan overall, where and how we are infected. Therefore this symposium focused on the risk of infection, source of infection, place of infection and direct estimation of the risk of infection in a place where risk is high.

1. The risk of infection in Japan: Takashi YOSHIYAMA (Fukujuji Hospital)

The annual risk of tuberculous infection (ARTI) is thought to be the best indicator to know the ongoing magnitude of tuberculosis. However, the tuberculin survey is difficult in Japan due to the high coverage of BCG and measurement of ARTI by interferon γ release assay (IGRA) requests huge sample population because the interval between the first baseline test and the second test need to be short due to the waning of IGRA after infection and the estimated ARTI is small in Japan. Therefore, upon the estimated incidence of infection by the tuberculin survey in 1968, and upon the hypothesis that the reduction speed of the risk of infection is in parallel with the reduction of the reported number of tuberculosis cases divided by the population among the young generation whose prevalence of infection is estimated to be lower than 10%, the risk of infection in Japan was estimated. The speed of the reduction of tuberculosis diseases was 2.6–3.7% in the age group of 20s and 30s and the estimated risk of infection was 0.36% in 1968 by the tuberculin survey and time trend extrapolation gives the figure of 0.05–0.07% in 2005.

2. Characteristics of index cases in TB transmission: Takeo INOUE (Aichi Shikatsu Health Center)

The subjects were 3,332 smear-positive (SP) patients, 2,139 smear-negative bacillus-positive (SN-BP) patients, 3,158 smear-negative bacillus-negative (SN-BN) patients, and 1,459 extra-pulmonary TB (EPTB) patients. Index cases were counted 337. Index case rates (ICRs) were 7.2% for SP patients, 2.1% for SN-BP patients, 1.2% for SN-BN patients, and 1.1% for EPTB patients. The differences were significant between SP patients and each of the other ($p < 0.001$), as well as between SP-BN patients and EPTB ($p < 0.05$). In SP patients, ICRs were significantly different between those aged 0–59 and those aged 60–99 (11.7% vs 4.4%), and the highest ICR was 14.1% in cavitory patients aged 0–59. In

SN-BP patients, the highest ICR was 10.3% in cavitory males aged 0–49, followed by 3.8% in non-cavitory females aged 0–49. TB epidemic were reported 109 in Japan between 2003 and 2005. ICRs were 0.46% for 87 SP cavitory patients, 0.10% for 15 SP non-cavitory patients, and 0.04% for 7 SN-BP patients. In the SP cavitory patients, ICRs were 2.32% for younger males aged 10–39, 0.37% for middle males aged 40–69, 0.41% for younger females, and 0.37% for middle females, showing significant differences between younger males and middle males, as well as between younger males and younger females ($p < 0.001$).

3. The Mode of transmission of *Mycobacterium tuberculosis* through DNA fingerprinting analysis in Okinawa Prefecture and Tokyo metropolitan: Akihiro OHKADO (Department of Research, The Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

Objective: To study the mode of transmission of *M. tuberculosis* through DNA fingerprinting analysis in Okinawa Prefecture and Tokyo metropolitan.

Results: 1,183 and 470 *M. tuberculosis* culture isolates (61% and 85.1% of bacillary positive tuberculosis patients registered in Okinawa Prefecture from 1996 to 2006, and in Shinjuku City from 2002 to 2007 respectively) were analyzed for IS6110 Restriction Fragment Length Polymorphism (RFLP). 135 genotype clusters from 516 patients in Okinawa, and 52 genotype clusters from 187 patients in Shinjuku were identified. The genotype-clustering rate was 43.6% and 39.8% in Okinawa and Shinjuku respectively. Transmission index of tuberculosis patients by the Incidence Rate Model was noted to be high among males in both areas; older age groups and residents of densely populated areas in Okinawa Prefecture; and among homeless people in Shinjuku City. 46 culture isolates of *M. tuberculosis*, the M-strain which had the following characters: 1) specific IS6110-RFLP band pattern with fourteen bands; 2) resistant to Streptomycin; 3) 2233–2517–3533–4243 or 2233–2517–3533–4253 profiles by 12MIRU 4ETR Variable Numbers of Tandem Repeats (VNTR), were identified from 46 tuberculosis patients in Tokyo Metropolitan. It was suggested that the strain with four copies of ETR-C tandem repeat spread widely and the transmission of this strain could be possibly link to the facilities where young people and tuberculosis high risk population, such as the homeless, were commonly staying.

4. Nosocomial tuberculosis infection in hospital with isolation wards for tuberculosis—Detection of tuberculosis infection

by using QuantiFERON®-TB Gold tests : Yoshiko KAWABE (National Hospital Organization Tokyo National Hospital, Kawabe Naika Clinic)

After removal to newly built hospital with facilities for nosocomial tuberculosis infection control in 2000, tuberculosis in health care worker had remarkably decreased in Tokyo National Hospital. In 2005, we have introduced QuantiFERON®-TB Gold (QFT) test in infection control program for the staff. The staff working at tuberculosis wards are checked QFT every 6–12 months, and the staff who are not working at tuberculosis wards are checked QFT at the event of contact to sputum smear positive patients. From 2005 to 2007, we observed 250 staff with following up QFT test. A nurse working at a tuberculosis ward suffered from tuberculosis. By following up QFT, an assistant nurse working at a tuberculosis ward and a nurse who contacted with a sputum smear positive tuberculosis patient at a ward for non-tuberculosis respiratory disease revealed positive conversion of the QFT. The mean observation period was 13.7 months and annual risk of infection was 1.05%. It is important for the detection of tuberculosis infection, to follow up QFT of health care workers working at tuberculosis wards and workers who had contact with smear positive tuberculosis patients.

5. Environmental factors relating to an outbreak of tuberculosis: Makoto TOYOTA (Kochi City Public Health Center)

To clarify environmental factors relating to an outbreak of tuberculosis, the ventilation rate within the room of the school was analyzed. Most of the windows of the building were of the fixed sash type, permitting only low ventilation ranging from about 1.6 to 1.8 room air change per hour. Low ventilation of the room and overcrowding contributed to an outbreak of tuberculosis.

6. Tuberculosis infection— Its perspectives in recent epidemiological studies and implications: Toru MORI (National Institute of Infectious Diseases)

As illustrated by an early works of Muench on a catalytic model, tuberculosis (TB) infection defined by the tuberculin skin test has been extensively studied in epidemiology mainly as a parameter of TB epidemics. Finally, Styblo established an idea of annual risk of infection as the most practical and valid epidemiological index of TB. However, tuberculin testing as its basis suffers from several drawbacks including low specificity due to BCG vaccination and environmental mycobacterial infections. This problem has been overcome by the advent of a new technology, i.e., the interferon-gamma release assay that is a coupling of the discovery of *Mycobacterium tuberculosis* specific antigens and the development of a simplified assay of interferon-gamma response.

In the recent advance in molecular technology a series of genotyping methods have been developed which have enabled to track transmissions of TB infection in a population. These technologies will provide the more precise qualitative images to TB epidemiology, while tuberculin test and IGRAs will describe its quantitative structures.

Key words: Tuberculosis infection, Risk of infection, Source, Endemic area

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————— The 83rd Annual Meeting Symposium —————

**PROGRESS OF MOLECULAR EPIDEMIOLOGY OF *MYCOBACTERIUM TUBERCULOSIS*
AND ITS APPLICATION FOR THE PREVENTION OF TUBERCULOSIS**

Chairpersons: ¹Atsushi HASE and ²Hideo MAEDA

Abstract: Recently, molecular biological studies of *Mycobacterium tuberculosis* have extremely developed. Especially, molecular epidemiological methods have been very useful tools for the study of active survey for the infection of tuberculosis. These techniques are useful not only to investigate transmission routes and infection sources, but also to analyze the prevalence in the area. In this symposium we have invited seven speakers who are talking about each titles as followed.

1. National tuberculosis genotyping and surveillance system in the Netherlands: An example of information system of tuberculosis genotyping from advanced countries in molecular epidemiology: Kazuhiro UCHIMURA (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

In the Netherlands, national tuberculosis genotyping and surveillance system is functioning well. The Royal Netherlands Tuberculosis Association (KNCV) keeps National Tuberculosis Register. The National Institute for Public Health and Environment (RIVM) performs genotyping and cluster analysis for all culture positive *M. tuberculosis* isolates. Since 1995, the National DNA fingerprinting surveillance project has routinely investigated the all genotyping patterns. Cluster information has been linked to the National Tuberculosis Register and has reported to Municipal Health Services (GGDs). There is a close relationship between GGDs, the KNCV and the RIVM to keep the national tuberculosis genotyping and surveillance system.

2. Molecular typing of *Mycobacterium tuberculosis* based on the variable numbers of tandem repeats (VNTR) used consensus loci: Shinji MAEDA, Yoshiro MURASE (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

The JATA (12) -VNTR analysis system was established for the molecular typing of *M. tuberculosis* in Japan. The typing degree of JATA (12) -VNTR was almost the same as that of RFLP analysis when the suspected cases of mass infection were examined. On the other hand, it was found that JATA (12) -VNTR system needed to improve the ability of typing for the molecular epidemiological analyses of population base.

3. Usefulness of *Mycobacterium tuberculosis* genotyping for tuberculosis control in Osaka Prefecture: Aki TAMARU (Bacteriology Division, Osaka Prefectural Institute of Public Health)

IS6110-RFLP genotyping of tuberculosis isolates has been used as a strategy for outbreak investigations and tracing the

transmissions of tuberculosis in Osaka Prefecture since 1995, where the incidence rate of TB is highest in Japan. However, there was limitation to apply this method for tuberculosis control because of 1) complicated analysis of RFLP patterns, 2) accumulation of identical patterns of RFLP (common clusters) in Osaka. On the contrary, the PCR-based genotyping, VNTR typing is rapid and simple to compare tuberculosis isolates. From the results of genotyping of 86 epidemic cases, there was good correspondence between 22 loci-VNTR typing and RFLP typing, furthermore the common clusters were subtyped by 22 loci-VNTR typing. Although standardization and quality assessment should be necessary for future investigation of tuberculosis, the application of 22 loci-VNTR typing is useful strategy for tuberculosis control in Osaka Prefecture.

4. Molecular epidemiological analysis of *M. tuberculosis* to implement the effective measures for tuberculosis prevention in the areas of low tuberculosis incidence: Eiji YOKOYAMA (Chiba Prefectural Institute of Public Health)

In the areas of low tuberculosis incidence, molecular epidemiological analysis of *M. tuberculosis* will contribute to implement the effective measures for tuberculosis prevention by the investigation of unapparent and/or uncertain transmission of the disease. VNTR analysis will be suitable for the molecular epidemiological analysis in the areas because a lot of VNTR data can be easily compared among different local governments.

5. Localization and Global Standardization of Genotyping by variable number of tandem repeats (VNTR) for TB: Takayuki WADA (Osaka City Institute of Public Health and Environmental Sciences)

The *M. tuberculosis* Beijing family strains in Japan were found to belong mainly to the ancient sublineage, in contrast to the worldwide evolutionary stream that led to the dominant modern sublineage. The singular epidemiologic pattern in Japan requires specific localized choice of loci of variable number of tandem repeats (VNTR) to apply the genotyping method efficiently to domestic molecular epidemiology. It is also necessary to follow global standards such as Supply's 15 (24) VNTR to meet international for future international comparison.

6. Implementation and evaluation by a population-based RFLP analysis in an urban area, Shinjuku City, Tokyo: Michiko NAGAMINE (Specific Disease Control Section,

Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government)

To examine *Mycobacterium tuberculosis* transmission patterns by RFLP analysis in Shinjuku, and to elucidate more effective methods of contact investigations. Clustering rates among homeless patients are high, therefore taking counter-measures for the homeless patients is an effective way. Introduction of RFLP analysis is a practical methodology to contact investigations. If RFLP analysis can be applied in a larger area, yearly changes of notification rates and molecular epidemiological clustering rates will provide indices for preventive measures against tuberculosis.

7. Utilization of molecular epidemiological data for improving TB control program in Kobe City : Chika SHIRAI (Department of Health and Welfare of Hyogo Ward), Riyo FUJIYAMA (Public Health Center of Kobe City), Tomotada IWAMOTO (Kobe Institute of Health)

Molecular epidemiological data by VNTR is a promising scientific evidence for the investigation of the transmission of TB, through the comparison between strains from new TB cases and past cases. We have developed the Kobe VNTR database including 894 TB cases for 5 years. The mission of Kobe city is to activate molecular epidemiology for improving TB control program.

Key words: Molecular epidemiology, Tuberculosis control, Genotyping, VNTR, RFLP

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